US04/38490

THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Application, Provisional Specification of the extract of Patent Application No.924/CHE/2003, dated 12/11/2003 by Dr. Reddy's Laboratories Ltd., an Indian Company registered under the Indian Companies Act, 1956, having its registered office at 7-1-27 Ameerpet, Hyderabad, Andhra Pradesh, India, 500 016.

.....

.....**In witness thereof**

I have hereunto set my hand

Dated this the 8th day of November 2004

M.S. Venkataraman

(M.S. VENKATARAMAN)
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

PATENT OFFICE BRANCH
GOVERNMENT OF INDIA
Guna Complex, 6th Floor, Annex.II
No.443, Anna Salai, Teynampet, Chennai – 600 018

FORM 1

THE PATENTS ACT, 1970
(39 of 1970)
APPLICATION FOR GRANT OF A PATENT
(Section 5(2), 7, 54 and 135 and Rule 33A)

1. We, Dr. Reddy's Laboratories Limited, an Indian company having its registered office at 7-1-27, Ameerpet, Hyderabad, Andhra Pradesh, INDIA, 500 016

2. (a) hereby declare that I/am/ we are in possession of an invention titled " **Novel process for the separation of Escitalopram from citalopram** ".

   (b) that the **Provisional/Complete** specification relating to this invention is filed with this application.

   (c) that there is no lawful ground of objection to the grant of a patent to me/us.

   further declare that the inventor(s) for the said invention are Vijayavitthal Thippannachar Mathad, Ghanta Mahesh Reddy, Govindan Shanmugam, Maddipatta Madhavi and Sundaram Venkataraman. All citizens & residents of India belonging to **Dr. Reddy's Laboratories Limited, 7-1-27, Ameerpet, Hyderabad – 500016, Andhra Pradesh.**

4. I/We claim the priority from the application(s) filed in convention countries, particulars of which are as follows.

5. I/We state that the said invention is an improvement in or modification of the invention, the particulars of which are as follows and of which I/We are the applicant/patantee

6. I/We state that the application is divided out of my/our application, the particulars of which are given below and pray that this application deemed to have been filed on _____ under section 16 of the Act.

7. That I/am/We are the assignee or legal representative of the true and first inventors.

8. That my/our address for service in India is as follows:

Sundaram Venkatraman,
Vice President-R&D
Dr. Reddy's Laboratories Limited
7-1-27, Ameerpet
Hyderabad, A.P., 500 016

9. Following declaration was given by the inventor(s) or applicant(s) in the convention country:

I/We, the true and first inventors for this invention or the applicant(s) in the convention country declare that the applicant(s) herein is/are my/our assignee or legal representative

(Signed) S. Venkatraman

Sundram Venkatraman
Plot No: 141; Flat No: 202
Sharadha Nilayam,
Mothi Nagar
Hyderabad-500 018

(Signed)

Vijayavitthal Thippannachar Mathad
114, Adithya homes, Adithya Nagar
Opp. JNTU, Pragathi Nagar Road
KPHB,
Hyderabad- 500 072.

(Signed) G.M. Reddy

Ghanta Mahesh Reddy,
Flat No. 408, Shruthi block
ROI'S Developers
Miyapur
Hyderabad-500 072

(Signed)

Govindan Shanmugam
MIG-79, Bharath Nagar colony
Hyderabad-500 018.

(Signed)

Maddipatta Madhavi
H.No. LIG B 393
Dr.A.S.Rao.Nagar
ECIL Post
Hyderabad-500062

10. That to the best of my/our knowledge, information and belief the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to me/us on this application.

11. Following are the attachments with the application
    (a) Provisional/Complete specification (-- 06 pages, in triplicate)
    (b) Drawings (---- pages, in triplicate)
    (c) Priority documents(s)
    (d) Statement and Undertaking on Form-3.
    (e) Power of authority
    (f) Abstract of the invention (---- page, in triplicate)
    (g) Fee Rs. 3000.00 (Three thousand rupees only) in Cash/cheque/bank draft bearing No. 327791 dated Oct. 31st 2003 drawn on HDFC Bank Limited, Lakdi-kapul, Hyderabad – 4.

I/We request that a patent may be granted to me/us for the said invention.

Dated this 6th of November 2003.

(Signed) S. Venkatraman

Sundaram Venkatraman,
Vice President-R&D
Dr. Reddy's Laboratories Limited.

To,
The Controller of Patents
The Patents Office Branch, Chennai.

FORM 2

THE PATENTS ACT, 1970

PROVISIONAL SPECIFICATION

(SECTION 10)

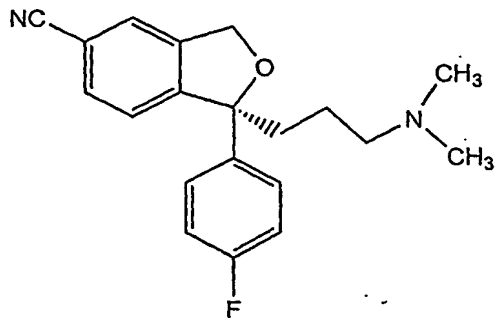
Novel process for the separation of Escitalopram from citalopram

Dr. Reddy's Laboratories Ltd.
an Indian Company having its registered office at
7-1-27, Ameerpet
Hyderabad – 500 016, A.P., India

The following specification particularly describes and ascertains the nature of this invention and the manner in which it is to be performed:

Field of the Invention:

The present invention relates to novel process for the separation of (S)-1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-sobenzofurancarbonitrile (escitalopram) acceptable salts from racemic Citalopram base or its pharmaceutically acceptable salts. Escitalopram can be shown as Formula (I).



Formula (I)

Escitalopram is well known as antidepressant agent of the selective serotonin reuptake inhibitor (SSRI).

Background of the Invention.

US 4,493,590 disclosed the process for the preparation of escitalopram in two different methods. Both methods involve the starting material as racemic diol.

First method comprises reaction of diol with optically active acid derivative to from a diastereomeric ester followed by separation on HPLC or fractional crystallization and followed by cyclization to afford the desired compound. On the other hand the second method comprises reacting the diol enantiomer with optically active acids to get diastereomeric salt followed by crystallization and converting into escitalopram.

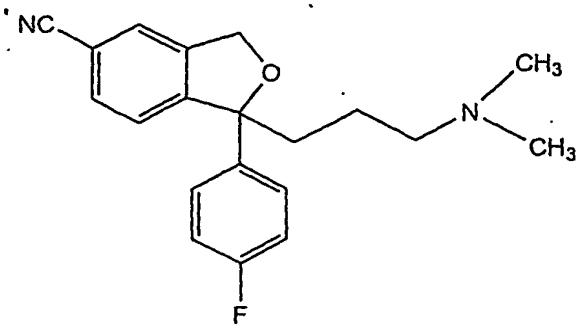
WO 03/051861A1 comprises the conversion of bromo-citalopram to the corresponding S-bromo-citalopram followed by cyanation to get the escitalopram.

It is noteworthy to mention that, the prior art literature clearly teaches that there is no direct chiral auxiliary technique by which one can separate S-enantiomer of citalopram from racemic citalopram.

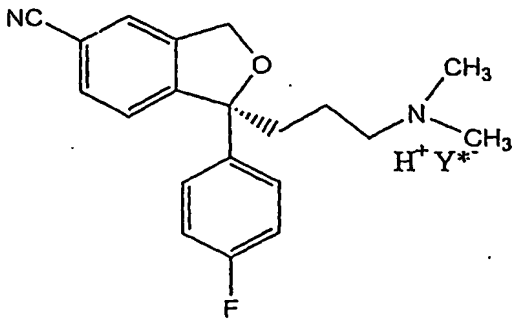
Summary of the Invention.

The present invention relates to novel process for the preparation of Escitalopram and/or its any salts from racemic Citalopram base or its salts. The process for the preparation of escitalopram and its pharmaceutically acceptable salts of the present invention comprises reaction of racemic Citalopram (II) with an enantiomerically enriched acid HY*, where Y* is chiral group to form diastereomeric salt (III) having Y* as counter ion, followed by hydrolysis of compound (III) to derive Escitalopram and further conversion to its pharmaceutically acceptable salts.

The present invention also relates to convert the pharmaceutically acceptable/ any salt of racemic Citalopram or racemic Citalopram free base by reacting with a base and then reacting with an enantiomerically enriched acid HY*, where Y* is chiral group to form diastereomeric salt (III) having Y* as counter ion, followed by hydrolysis of compound (III) to get Escitalopram.



Formula (II)



Formula (III)

Detailed description of the invention:

The racemic compound of formula (II) as a free base is resolved by making its salt with a chiral auxiliary to get a pair of diastereomers which are separated by fractional crystallization. The diastereomeric salt can be formed by reacting with optically active acids such as tartaric acid, di-p-toluoyl tartaric acid, camphorsulphonic acid, malic acid, N-acetyl glutamic acid, mandelic acid and the like.

The formation, fractional crystallization and isolation of diastereomeric salt is carried out in aqueous organic solvents such as a mixture of alcohol-water, ketone-water and acetonitrile-water and the like. As a result two diastereomeric salts can be separated due to difference in solubility and stability properties. The required salt is hydrolyzed with any base, like alkaline hydroxide or organic base to afford the free base of Escitalopram as oil. The obtained oil is further purified optionally into a crystalline solid. Then after escitalopram freebase as oil or a crystalline solid is converted in to pharmaceutically acceptable salt by conventional known methods.

Process for the preparation of Escitalopram and its pharmaceutically acceptable salts

The main aspect of the present invention is related to novel process for the preparation of Escitalopram and its pharmaceutically acceptable salts from racemic Citalopram base or its pharmaceutically acceptable/any salts, which comprises:

i) Converting racemic citalopram pharmaceutically acceptable salt or any salt, in to its free base with a base selected from any organic or inorganic bases and a suitable organic solvent;

ii) separating of the organic layer of step (i) followed by concentrating the obtained layer to afford the residual mass;

iii) stirring the residual mass of step (ii) in a desired organic solvent to obtain a solid mass;

iv) Filtering and drying the solid mass obtained in step (iii) by conventional methods;

v) Converting the free base obtained in step (iv) in to diastereomeric salts with an optically active acids such as tartaric acid, di-p-toluyl tartaric acid, camphorsulphonic acid, malic acid, N-acetyl glutamic acid or mandelic acid and the like in a suitable solvent system such as mixture of organic solvents or aqueous organic solvents;

vi) hydrolyzing the the required diastereoisomer obtained in step (v) using base to get Escitalopram free base as oil;

vii) optionally isolating the free base obtained as an oil in step (vi) to a crystalline solid by a purification in a suitable solvent

viii) converting escitalopram free base to its pharmaceutically acceptable salts, in known conventional methods.

Dated: 06th of November 2003

Signed) S. Venkataraman
Sundaram Venkataraman,
Vice-President (R&D),
Dr. Reddy's Laboratories Limited.